Estradiol Matrix
Transdermal Delivery System
NDA 21-310

Package Insert

Watson Laboratories Inc.
Research Park
417 Wakara Way
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Alora®
(estradiol transdermal system)
Continuous Delivery for Twice Weekly Dosing

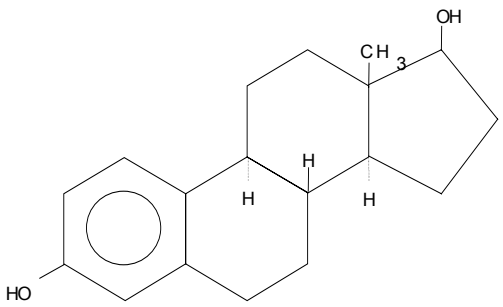
PRESCRIBING INFORMATION

ESTROGENS INCREASE THE RISK OF ENDOMETRIAL CANCER.

Close clinical surveillance of all women taking estrogens is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is currently no evidence that the use of "natural" estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose.

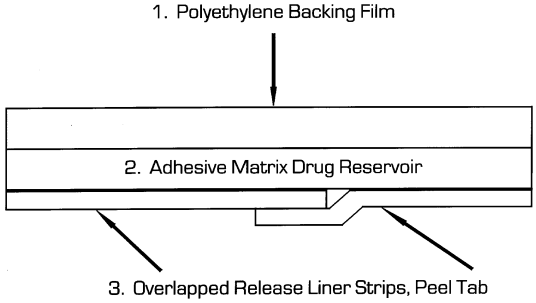
DESCRIPTION

Alora (estradiol transdermal system) is designed to deliver estradiol continuously and consistently over a 3 or 4-day interval upon application to intact skin. Four strengths of **Alora** are available, having nominal *in vivo* delivery rates of 0.025, 0.05, 0.075, and 0.1 mg estradiol per day through skin of average permeability (inter-individual variation in skin permeability is approximately 20%). **Alora** has contact surface areas of 9, 18, 27, and 36 cm^2 and contains 0.75, 1.5, 2.3, and 3.0 mg of estradiol, USP, respectively. The composition of the estradiol transdermal systems per unit area is identical. Estradiol, USP is a white, crystalline powder that is chemically described as estra-1,3,5(10)-triene-3, 17ß-diol, has an empirical formula of $C_{18}H_{24}O_2$ and has molecular weight of 272.39. The structural formula is:



Estradiol

Alora consists of three layers. Proceeding from the polyethylene backing film as shown in the cross-sectional view below, the adhesive matrix drug reservoir that is in contact with the skin consists of estradiol, USP and sorbitan monooleate dissolved in an acrylic adhesive matrix. The polyester overlapped release liner protects the adhesive matrix during storage and is removed prior to application of the system to the skin.



CLINICAL PHARMACOLOGY

Estrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than its metabolites, estrone and estriol, at the receptor level. The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70 to 500 μg of estradiol daily, depending on the phase of the menstrual cycle. After menopause, most endogenous estrogen is produced by conversion of androstenedione, secreted by the adrenal cortex, to estrone by peripheral tissues. Thus, estrone and the sulfate conjugated form, estrone sulfate, are the most abundant circulating estrogens in postmenopausal women.

Estrogens act through binding to nuclear receptors in estrogen-responsive tissues. To date, two estrogen receptors have been identified. These vary in proportion from tissue to tissue. Circulating estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone (LH) and follicle stimulating hormone (FSH) through a negative feedback mechanism. Estrogen replacement therapy acts to reduce the elevated levels of these hormones seen in postmenopausal women.

Pharmacokinetics

The skin metabolizes estradiol only to a small extent. In contrast, orally administered estradiol is rapidly metabolized by the liver to estrone and its conjugates, giving rise to higher circulating levels of estrone than estradiol. Therefore, transdermal administration produces therapeutic plasma levels of estradiol with lower levels of estrone and estrone conjugates and requires smaller total doses than does oral therapy.

Absorption

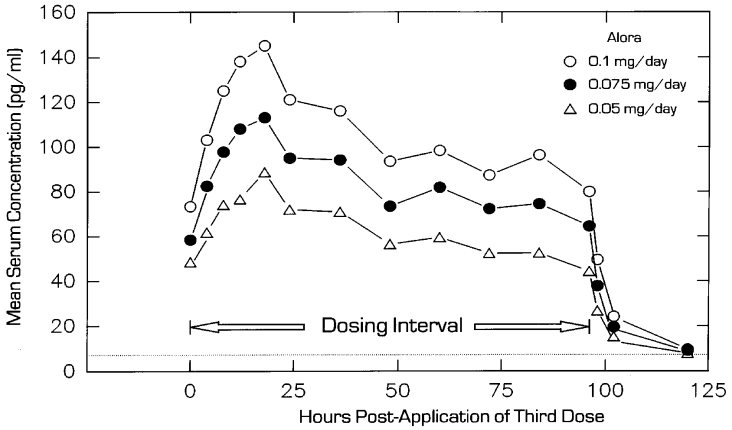
Estradiol is transported across intact skin and into the systemic circulation by a passive diffusion process, the rate of diffusion across the stratum corneum being the principal factor. **Alora** presents sufficient concentration of estradiol to the surface of the skin to maintain continuous transport over the 3 to 4 day dosing interval.

Direct measurement of total absorbed dose of estradiol through analysis of residual estradiol content of systems worn over a continuous four day interval during 251 separate occasions in 123 postmenopausal women demonstrated that the average daily dose absorbed from **Alora** was 0.003 ± 0.001 mg estradiol per cm^2 active surface area. The nominal mean *in vivo* daily delivery rates of estradiol calculated from these data are 0.027 mg/day, 0.054 mg/day, 0.081 mg/day, and 0.11 mg/day for the 9 cm^2, 18 cm^2, 27 cm^2, and 36 cm^2 **Alora**, respectively.

In another study, 20 women also were treated with three consecutive doses of **Alora** 0.05 mg/day, **Alora** 0.075 mg/day and **Alora** 0.1 mg/day on abdominal application sites. Mean steady state estradiol serum concentrations observed over the dosing interval are shown in Figure 1.

Figure 1

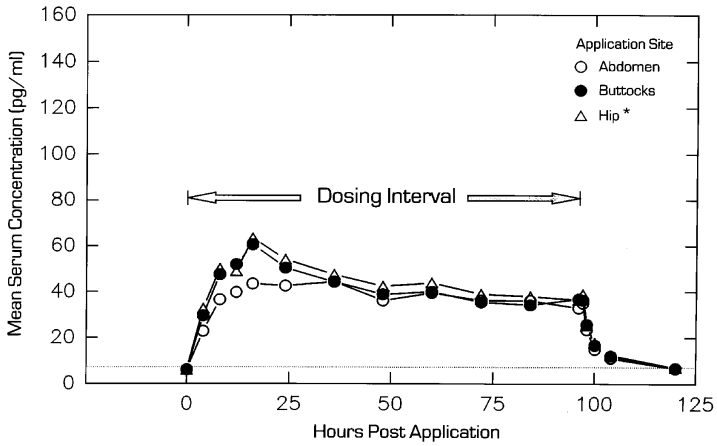
Mean steady state estradiol serum concentration during the third twice weekly dose of **Alora** 0.1 mg/day, **Alora** 0.075 mg/day, and **Alora** 0.05 mg/day in 20 postmenopausal women.



In a single dose randomized crossover study conducted to compare the effect of site of **Alora** application, 31 postmenopausal women wore single **Alora** 0.05 mg/day for four day periods on the lower abdomen, upper quadrant of the buttocks, and outside aspect of the hip. The estradiol serum concentration profiles are shown in Figure 2.

Figure 2

Mean estradiol serum concentrations during a single 4-day wearing of **Alora** 0.05 mg/day applied by 31 postmenopausal women to the lower abdomen, upper quadrant of the buttocks or outer aspect of the hip.



*C_{max} and C_{avg} statistically different from abdomen

Table 1 provides a summary of the estradiol pharmacokinetic parameters studied during biopharmaceutic evaluation of **Alora**.

Table 1

Mean (SD) Pharmacokinetic Profile of **Alora** Over an 84-Hour Dosing Interval

Alora (mg/day)	Application Site	N	Dosing	C_{max} (pg/ml)	C_{min} (pg/ml)	C_{avg} (pg/ml)	CL (L/hr)
0.05	Abdomen	20	Multiple	92 (33)	43 (12)	64 (19)	54 (18)
0.075	Abdomen	20	Multiple	120 (60)	53 (23)	86 (40)	53 (12)
0.1	Abdomen	42	Multiple	144 (57)	58 (20)	98 (38)	61 (18)
0.05	Abdomen	31	Single	53 (23)	-	41 (18)	69 (22)
	Buttock	31	Single	67 (45)	-	45 (21)	66 (23)
	Hip*	31	Single	69 (30)	-	48 (17)	62 (18)

* C_{max} and C_{avg} statistically different from abdomen

Steady state estradiol serum concentrations were measured in two well-controlled clinical trials in the treatment of menopausal symptoms of 3 month duration (Studies 1 and 2), and one trial in the prevention of postmenopausal osteoporosis of 2 year duration (Study 3). Table 2 provides a summary of these data.

Table 2

Mean (SD) steady-state estradiol serum concentrations (pg/ml) in clinical trials of 3 month (Studies 1 and 2) and 2 year (Study 3) duration

Alora (mg/day)	Study 1	Study 2	Study 3
0.025	-	-	24.5 (12.4)
0.05	46.9 (38.5)	38.8 (38.0)	42.6 (23.7)
0.075	-	-	56.7 (36.8)
0.1	99.2 (77.0)	97.0 (87.5)	-

In a 2-year, randomized, double-blind, placebo-controlled, prevention of postmenopausal osteoporosis study in 355 hysterectomized women, the average baseline-adjusted steady-state estradiol serum concentrations were 18.6 pg/ml (45 patients) for the 0.025 mg/day dose, 35.9 pg/ml (47 patients) for the 0.05 mg/day dose and 50.1 pg/ml (46 patients) for the 0.075 mg/day dose. These values were linearly related and dose proportional.

Distribution

No specific investigation of the tissue distribution of estradiol absorbed from **Alora** in humans has been conducted. The distribution of exogenous estrogens is similar to that of endogenous estrogens. Estrogens are widely distributed in the body and are generally found in higher concentrations in the sex hormone target organs. Estrogens circulate in the blood largely bound to sex hormone binding globulin (SHBG) and albumin.

Metabolism

Exogenous estrogens are metabolized in the same manner as endogenous estrogens. Circulating estrogens exist in a dynamic equilibrium of metabolic interconversions. These transformations take place mainly in the liver. Estradiol is converted reversibly to estrone, and both can be converted to estriol, which is the major urinary metabolite. Estrogens also undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the gut followed by reabsorption. In

postmenopausal women a significant portion of the circulating estrogens exist as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogens.

Excretion
Estradiol, estrone and estriol are excreted in the urine along with glucuronide and sulfate conjugates. The apparent mean (SD) serum half-life of estradiol determined from biopharmaceutic studies conducted with Alora is 1.75 ± 2.87 hours.

Special Populations
Alora has been studied only in healthy postmenopausal women (approximately 90% Caucasian). There are no long term studies in postmenopausal women with an intact uterus. No pharmacokinetic studies were conducted in other special populations, including patients with renal or hepatic impairment.

Drug Interactions
In vitro and *in vivo* studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4 such as St. John's Wort preparations (Hypericum perforatum), phenobarbital, phenytoin, carbamazepine, rifampin and dexamethasone may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4 such as cimetidine, erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir, and grapefruit juice may increase plasma concentrations of estrogens and may result in side effects.

Adhesion
The adhesion potential of **Alora** was evaluated in a randomized clinical trial involving 408 healthy postmenopausal women who wore placebo systems corresponding to the 18 cm^2 size **Alora**. The placebos were applied twice weekly for 4 weeks on the lower quadrant of the abdomen. It should be noted that the lower abdomen, the upper quadrant of the buttocks or outer aspect of the hip are the approved sites of application for **Alora**. Subjects were instructed not to do strenuous activities, take baths, use hot tubs or swim. In 968 observations, there was a partial or complete adhesion rate of approximately 97%. The total detachment rate was approximately 3%. Adhesion potentials of the 9 cm^2, 27 cm^2 and 36 cm^2 sizes of **Alora** have not been studied.

CLINICAL STUDIES

Effects on vasomotor symptoms
Efficacy of **Alora** has been studied in a double blind/double dummy, randomized, parallel group, placebo-controlled trial involving a total of 268 postmenopausal women over a 12-week dosing period. Only women having estradiol and FSH serum concentrations in the postmenopausal range and who exhibited a weekly average of at least 60 moderate-to-severe hot flushes during the screening period were enrolled in the studies.

Patients received **Alora** 0.05 mg/day and a placebo system or **Alora** 0.1 mg/day and a placebo system, or two placebo systems dosed twice weekly over a 12-week duration. Measures of efficacy included mean reduction in weekly number of moderate-to-severe vasomotor symptoms when compared to the mean baseline average determined during a 2-week pre-dosing screening period. **Alora** was shown to be statistically better than placebo at Weeks 4 and 12 for relief of both the frequency (see Table 3) and severity of vasomotor symptoms.

Table 3

Mean Change from Baseline in Frequency of Moderate-to-Severe Vasomotor Symptoms for **Alora** Compared to Placebo (ITT)

Week of Therapy	Mean Change from Baseline		
	Alora 0.05 mg/day N = 87 Baseline = 90	**Alora** 0.1 mg/day N = 91 Baseline = 85	Placebo N = 90 Baseline = 92
4 *	- 57	- 70	- 45
8	- 65	- 77	- 49
12 *	- 68	- 79	- 54

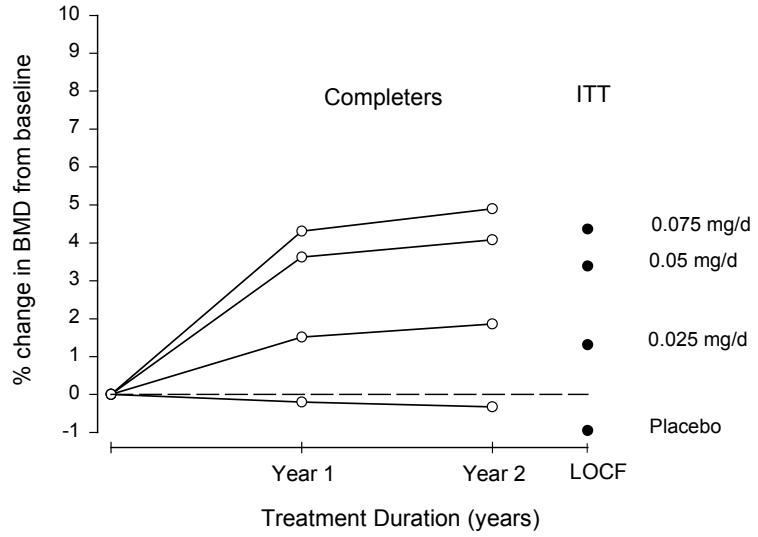
*Indicates statistically significant differences between both strengths of Alora and placebo using an ANCOVA model adjusting for baseline.

Effects on vulvar and vaginal atrophy
Vaginal cytology was obtained pre-dosing and at last visit in 54 women treated with **Alora** 0.05 mg/day, in 45 women treated with **Alora** 0.1 mg/day and in 46 women in the placebo group. Superficial cells increased by a mean of 18.7%, 23.7% and 8.7% for the **Alora** 0.05 mg/day, **Alora** 0.1 mg/day, and placebo groups, respectively. Corresponding reductions in basal/parabasal and intermediate cells were also observed.

Effects on bone mineral density
Lumbar spine bone mineral density (BMD) was measured by DEXA in a two-year, randomized, multi-center, double-blind, placebo-controlled, study in 355 hysterectomized, non-osteoporotic women (i.e., T-scores > -2.5). Eighty-six percent of the women were Caucasian, the mean age was 53.2 years (range 26 to 69), and the average number of years since menopause (natural or surgical) was not determined. Three Alora doses (0.025, 0.05 and 0.075 mg/day) were compared to placebo in terms of the % change in BMD from baseline to Year 2. The systems were applied every 3 or 4 days on alternate sides of the lower abdomen. All patients received 1000 mg of oral elemental calcium daily. The average baseline lumbar spine T-score was -0.64 (range -2.7 to 3.8). The % changes in BMD from baseline are illustrated in Figure 3.

Figure 3

Mean % change in BMD from baseline at 1 and 2 years after initiation of therapy with Placebo and Alora 0.025, 0.05 and 0.075 mg/day in the completer and intent-to-treat population with last observation carried forward (LOCF)



A total of 196 patients (44 – 0.025 mg/d, 49 – 0.050 mg/d, 45 – 0.075 mg/d, and 58 – placebo) were included in the completer population compared with 258 patients (59 – 0.025 mg/d, 64 – 0.050 mg/d, 63 – 0.075 mg/d, and 72 – placebo) in the intent-to-treat, last observation carried forward population.

All **Alora** doses were statistically superior to placebo for the primary endpoint, percent change in BMD from baseline. The mean 2-year (LOCF) percent changes in BMD for 0.025 mg/d, 0.05 mg/d, 0.075 mg/d, and placebo were 1.45%, 3.39%, 4.24%, and –0.80% respectively.

INDICATIONS AND USAGE

Alora is indicated in:

1. Treatment of moderate-to-severe vasomotor symptoms associated with the menopause.
2. Treatment of vulvar and vaginal atrophy.
3. Treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure.
4. Prevention of postmenopausal osteoporosis. Estrogen replacement therapy reduces bone resorption and retards postmenopausal bone loss. When estrogen therapy is discontinued, bone mass declines at a rate comparable to that of the immediate postmenopausal period.

   The mainstays of prevention of postmenopausal osteoporosis are weight-bearing exercise, adequate calcium and vitamin D intake and, when indicated, estrogen. Postmenopausal women absorb dietary calcium less efficiently than premenopausal women and require an average of 1500 mg/day of elemental calcium to remain in neutral calcium balance. The average calcium intake in the US is 400-600 mg/day. Therefore, when not contraindicated, calcium supplementation may be helpful for women with suboptimal dietary intake. Vitamin D supplementation of 400-800 IU/day may also be required to ensure adequate daily intake in postmenopausal women.

Risk factors for postmenopausal osteoporosis include early menopause, moderately low bone mass, thin body build, Caucasian or Asian race, family history of osteoporosis, and lifestyle (sedentary exercise habits, cigarette smoking and alcohol abuse).

CONTRAINDICATIONS

Estrogens should not be used in individuals with any of the following conditions:

1. Known or suspected pregnancy; see **PRECAUTIONS.** Estrogens may cause fetal harm when administered to a pregnant woman.
2. Undiagnosed abnormal genital bleeding;
3. Known or suspected cancer of the breast;
4. Known or suspected estrogen-dependent neoplasia;
5. Active deep vein thrombosis/pulmonary embolism or a history of these conditions.
6. Known hypersensitivity to any of the components of **Alora**.

WARNINGS

1. Induction of Malignant Neoplasms.

a. ***Endometrial cancer***. The reported endometrial cancer risk among unopposed estrogen users is about 2 to 12-fold greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than one year. The greatest risk appears associated with prolonged use, with increased risks of 15 to 24-fold for five to ten years or more, and this risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued.

b. ***Breast cancer***. While some epidemiologic studies suggest a very modest increase in breast cancer risk for estrogen-alone users versus non-users, other studies have not shown any increased risk. The addition of progestin to estrogen may increase the risk for breast cancer over that noted in non-hormone users more significantly (by about 24 to 40%), although this is based solely on epidemiologic studies, and definitive conclusions await prospective, controlled clinical trials.

Women without a uterus who require hormone replacement should receive estrogen-alone therapy, and should not be exposed unnecessarily to progestins. Women with a uterus who are candidates for short-term combination estrogen/progestin therapy (for relief of vasomotor symptoms) are not felt to be at a substantially increased risk for breast cancer. Women with a uterus who are candidates for long-term use of estrogen/progestin therapy should be advised of potential benefits and risks (including the potential for an increased risk of breast cancer).

All women should receive yearly breast exams by a health-care provider and perform monthly breast-self examinations. In addition, mammography examinations should be scheduled as suggested by providers based on patient age and risk factors.

2. Thromboembolic Disorders

The physician should be aware of the possibility of thrombotic disorders (thrombophlebitis, retinal thrombosis, cerebral embolism, and pulmonary embolism) during estrogen replacement therapy and be alert to their earliest manifestations. Should any of these occur or be suspected, estrogen replacement therapy should be discontinued immediately. Patients who have risk factors for thrombotic disorders should be kept under careful observation.

Venous thromboembolism. Several epidemiologic studies have found an increased risk of venous thromboembolism (VTE) in users of estrogen replacement therapy (ERT) who did not have predisposing conditions for VTE, such as past history of cardiovascular disease or a recent history of pregnancy,

surgery, trauma, or serious illness. The increased risk was found only in current ERT users; it did not persist in former users. The risk appeared to be higher in the first year of use and decreased thereafter. The findings were similar for ERT alone or with added progestin and pertain to commonly used oral and transdermal doses, with a possible dose-dependent effect on risk. The studies found the VTE risk to be about one case per 10,000 women per year among women not using ERT and without predisposing conditions. The risk in current ERT users was increased to 2 to 3 cases per 10,000 women per year.

Cerebrovascular disease. Embolic cerebrovascular events have been reported in postmenopausal women receiving estrogens.

Cardiovascular disease. Large doses of estrogen (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown in a large prospective clinical trial in men to increase the risks of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis.

3. **Gallbladder Disease.** A 2 to 4-fold increase in the risk of gallbladder disease requiring surgery in postmenopausal women receiving estrogens has been reported.

4. **Hypercalcemia**. Estrogen administration may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If hypercalcemia occurs, use of the drug should be stopped and appropriate measures should be taken to reduce the serum calcium level.

PRECAUTIONS

A. General

1. ***Addition of a progestin when a woman has not had a hysterectomy.*** Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer.

   There are, however, possible risks that may be associated with the use of progestins in estrogen replacement regimens. These include adverse effects on lipoprotein metabolism (e.g., lowering HDL and raising LDL) and impairment of glucose tolerance. The choice of progestin, its dose, and its regimen may be important in minimizing these adverse effects.

2. ***Cardiovascular risk***. The effects of estrogen replacement on the risk of cardiovascular disease have not been adequately studied. However, data from the Heart and Estrogen/Progestin Replacement Study (HERS), a controlled clinical trial of secondary prevention of 2,763 post-menopausal women with documented heart disease, demonstrated no benefit. During an average follow-up of 4.1 years, treatment with oral conjugated estrogen plus medroxyprogesterone acetate did not reduce the overall rate of coronary heart disease (CHD) events in postmenopausal women with established coronary disease. There were more CHD events in the hormone treated group than in the placebo group in year 1, but fewer events in years 3 through 5.

3. ***Elevated blood pressure***. In a small number of case reports, substantial increases in blood pressure during estrogen replacement therapy have been attributed to idiosyncratic reactions to estrogens. In a large, randomized, placebo controlled clinical trial, a generalized effect of estrogen therapy on blood pressure was not seen.

4. ***Familial hyperlipoproteinemia***. In patients with familial defects of lipoprotein metabolism, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis and other complications

5. ***Impaired liver function***. Estrogens may be poorly metabolized in patients with impaired liver function.

6. ***Hypothyroidism***. Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Patients with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T4 and T3 serum concentrations in the normal range. Patients dependent on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of their thyroid replacement therapy. These patients should have their thyroid function monitored in order to maintain their free thyroid hormone levels in an acceptable range.

7. ***Fluid retention***. Because estrogens may cause some degree of fluid retention, conditions which might be influenced by this factor, such as asthma, epilepsy, migraine and cardiac or renal dysfunction, warrant careful observation when estrogens are prescribed.

8. ***Exacerbation of endometriosis***. Endometriosis may be exacerbated with administration of estrogen therapy.

9. ***Hypocalcemia***. Estrogens should be used with caution in individuals with severe hypocalcemia.

B. Patient Information

See text of Patient Information after the **HOW SUPPLIED** section.

C. Laboratory Tests

Estrogen administration should be guided by clinical response at the lowest dose for the treatment of vasomotor symptoms and vulvar and vaginal atrophy. Laboratory parameters may be useful in guiding dosage for the treatment of hypoestrogenism due to hypogonadism, castration and primary ovarian failure.

D. Drug/Laboratory Test Interactions

1. Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, and beta-thromboglobulin; decreased levels of anti-factor Xa and antithrombin III, decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.

2. Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 levels (by column or by radioimmunoassay) or T3 levels by radioimmunoassay. T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 and free T3 concentrations are unaltered.

3. Other binding proteins may be elevated in serum, i.e., corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG), leading to increased circulating corticosteroids and sex steroids, respectively. Free or biologically active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).

4. Increased plasma HDL and HDL-2 subfraction concentrations, reduced LDL cholesterol concentration, increased triglycerides levels.

5. Impaired glucose tolerance.

6. Reduced response to the metapyrone test.

7. Reduced serum folate concentration.

E. Carcinogenesis, Mutagenesis, Impairment Of Fertility
Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and liver. (See **CONTRAINDICATIONS**)

F. Pregnancy Category X
Alora should not be used during pregnancy. See **CONTRAINDICATIONS**.

G. Nursing Mothers
The administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk. In addition, estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the milk. Estrogens are not indicated for the prevention of postpartum breast engorgement.

H. Pediatric Use.
Estrogen replacement therapy has been used for the induction of puberty in adolescents with some forms of pubertal delay. Safety and effectiveness in pediatric patients have not otherwise been established.

Large and repeated doses of estrogen over an extended time period have been shown to accelerate epiphyseal closure, which could result in short adult stature if treatment is initiated before the completion of physiologic puberty in normally developing children. If estrogen is administered to patients whose bone growth is not complete, periodic monitoring of bone maturation and effects on epiphyseal centers is recommended during estrogen administration.

Estrogen treatment of prepubertal girls also induces premature breast development and vaginal cornification, and may induce gynecomastia. See **INDICATIONS** and **DOSAGE AND ADMINISTRATION** sections.

I. Geriatric Use
Clinical studies of **Alora** did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS
Because clinical trials are conducted under widely varying conditions, adverse reactions rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

See **WARNINGS** regarding induction of malignant neoplasms, thromboembolic disorders, gallbladder disease, and hypercalcemia. See **PRECAUTIONS** regarding cardiovascular risk and elevated blood pressure.

Incidence of adverse events > 2% of each treatment group is given in Table 4.

Table 4

Incidence of Adverse Events > 2% for Alora and Placebo Systems
(data are expressed as N and (%) of treatment group)

Body System Preferred Term	Placebo[a] (N=87)	Alora[a] 0.025 mg/day (N=89)	Alora[a] 0.05 mg/day (N=90)	Alora[a] 0.075 mg/day (N=89)	Alora[b] 0.1 mg/day (N=174)
Body As A Whole					
Accidental Injury	4 (4.6)	6 (6.7)	8 (8.9)	4 (4.5)	9 (5.2)
Allergic Reaction	2 (2.3)	4 (4.5)	4 (4.4)	2 (2.2)	1 (0.6)
Asthenia	4 (4.6)	7 (7.9)	4 (4.4)	0 (0)	4 (2.3)
Cyst	3 (3.4)	0 (0)	6 (6.7)	3 (3.4)	0 (0)
Flu Syndrome	9 (10.3)	8 (9)	12 (13.3)	9 (10.1)	6 (3.4)
Headache	11 (12.6)	10 (11.2)	8 (8.9)	5 (5.6)	37 (21.3)
Infection	2 (2.3)	2 (2.2)	3 (3.3)	3 (3.4)	2 (1.1)
Infection Fungal	1 (1.1)	3 (3.4)	9 (10)	4 (4.5)	0 (0)
Pain	11 (12.6)	9 (10.1)	5 (5.6)	6 (6.7)	16 (9.2)
Pain Abdominal	4 (4.6)	7 (7.9)	5 (5.6)	1 (1.1)	5 (2.9)
Pain Back	5 (5.7)	5 (5.6)	3 (3.3)	7 (7.9)	11 (6.3)
Pain Chest	4 (4.6)	4 (4.5)	2 (2.2)	1 (1.1)	2 (1.1)
Cardiovascular					
Hypertension	3 (3.4)	3 (3.4)	3 (3.3)	6 (6.7)	0 (0)
Migraine	2 (2.3)	6 (6.7)	2 (2.2)	0 (0)	2 (1.1)
Vasodilation	13 (14.9)	6 (6.7)	2 (2.2)	1 (1.1)	0 (0)
Digestive					
Constipation	4 (4.6)	3 (3.4)	6 (6.7)	1 (1.1)	3 (1.7)
Diarrhea	2 (2.3)	1 (1.1)	3 (3.3)	2 (2.2)	5 (2.9)
Dyspepsia	1 (1.1)	8 (9)	4 (4.4)	3 (3.4)	2 (1.1)
Flatulence	5 (5.7)	1 (1.1)	2 (2.2)	3 (3.4)	8 (4.6)
Gastroenteritis	2 (2.3)	3 (3.4)	4 (4.4)	3 (3.4)	0 (0)
Nausea	3 (3.4)	6 (6.7)	5 (5.6)	3 (3.4)	7 (4)
Metabolic And Nutritional					
Edema Peripheral	4 (4.6)	3 (3.4)	4 (4.4)	3 (3.4)	3 (1.7)
Weight Increased	4 (4.6)	3 (3.4)	2 (2.2)	4 (4.5)	1 (0.6)
Musculoskeletal					
Arthralgia	12 (13.8)	5 (5.6)	10 (11.1)	11 (12.4)	2 (1.1)
Bone Fracture Spontaneous	7 (8)	1 (1.1)	3 (3.3)	0 (0)	0 (0)
Joint Disorder	2 (2.3)	4 (4.5)	4 (4.4)	1 (1.1)	0 (0)
Myalgia	4 (4.6)	3 (3.4)	2 (2.2)	5 (5.6)	3 (1.7)
Nervous					
Anxiety	3 (3.4)	0 (0)	9 (10)	2 (2.2)	3 (1.7)
Depression	8 (9.2)	1 (1.1)	3 (3.3)	1 (1.1)	6 (3.4)
Dizziness	0 (0)	1 (1.1)	7 (7.8)	4 (4.5)	1 (0.6)
Hypesthesia	2 (2.3)	3 (3.4)	3 (3.3)	0 (0)	0 (0)
Insomnia	7 (8)	4 (4.5)	2 (2.2)	1 (1.1)	8 (4.6)

Body System Preferred Term	Placebo[a] (N=87)	Alora[a] 0.025 mg/day (N=89)	Alora[a] 0.05 mg/day (N=90)	Alora[a] 0.075 mg/day (N=89)	Alora[b] 0.1 mg/day (N=174)
Respiratory					
Asthma	1 (1.1)	3 (3.4)	3 (3.3)	1 (1.1)	2 (1.1)
Bronchitis	6 (6.9)	7 (7.9)	4 (4.4)	4 (4.5)	6 (3.4)
Cough Increased	2 (2.3)	1 (1.1)	4 (4.4)	1 (1.1)	6 (3.4)
Infection Respiratory	23 (26.4)	22 (24.7)	22 (24.4)	19 (21.3)	28 (16.1)
Pharyngitis	1 (1.1)	4 (4.5)	2 (2.2)	2 (2.2)	4 (2.3)
Pneumonia	4 (4.6)	4 (4.5)	4 (4.4)	1 (1.1)	1 (0.6)
Sinusitis	16 (18.4)	9 (10.1)	11 (12.2)	6 (6.7)	13 (7.5)
Skin					
Application Site Reaction	51 (58.6)	47 (52.8)	51 (56.7)	49 (55.1)	10 (5.7)
Hirsutism	0 (0)	2 (2.2)	2 (2.2)	4 (4.5)	1 (0.6)
Pruritus	4 (4.6)	2 (2.2)	1 (1.1)	6 (6.7)	9 (5.2)
Rash	5 (5.7)	6 (6.7)	8 (8.9)	4 (4.5)	5 (2.9)
Special Senses					
Conjunctivitis	2 (2.3)	2 (2.2)	3 (3.3)	2 (2.2)	0 (0)
Otitis Media	2 (2.3)	3 (3.4)	2 (2.2)	1 (1.1)	0 (0)
Urogenital					
Breast Enlargement	3 (3.4)	1 (1.1)	2 (2.2)	6 (6.7)	4 (2.3)
Infection Urinary Tract	2 (2.3)	5 (5.6)	4 (4.4)	2 (2.2)	3 (1.7)
Leukorrhea	1 (1.1)	3 (3.4)	2 (2.2)	4 (4.5)	3 (1.7)
Neoplasm Breast	6 (6.9)	3 (3.4)	5 (5.6)	1 (1.1)	3 (1.7)
Pain Breast	7 (8)	13 (14.6)	16 (17.8)	31 (34.8)	12 (6.9)
Vaginitis	6 (6.9)	0 (0)	3 (3.3)	0 (0)	14 (8)
Vaginal Bleeding[c]	4 (12.9)	NA	6 (8.7)	NA	29 (33.3)

a – Adverse events for the three lower Alora doses and placebo were obtained from the two year prevention of osteoporosis study
b – Adverse events for the highest Alora dose were obtained from two 12-week studies of the treatment of menopausal symptoms
c – Data reported for women with partially or fully intact uteri in the menopausal symptom study only (N=31 for Placebo; N=69 for Alora 0.05 mg/day and N=87 for Alora 0.1 mg/day)
NA – data not available

OVERDOSAGE

Serious ill effects have not been reported following acute ingestion of large doses of estrogen containing oral contraceptives by young children. Overdosage of estrogen may cause nausea and vomiting, and withdrawal bleeding may occur in females.

DOSAGE AND ADMINISTRATION

Alora should be administered twice weekly, as instructed. The adhesive side of the **Alora** system should be placed on a clean, dry area of skin. The recommended application site is the lower abdomen. In addition, the upper quadrant of the buttocks or outer aspect of the hip may be used. **Alora** ***should not be applied to the breasts***. The sites of application should be rotated, with an interval of at least 1 week allowed between applications to a particular site. The area selected should not be oily, damaged, or irritated. The waistline should be avoided, since tight clothing may rub the system off. The system should be applied immediately after opening the pouch and removing the protective liner. The system should be pressed firmly in place with the palm of the hand for about 10 seconds, making sure there is good contact, especially around the edges.

In the event that a system should fall off, the same system may be reapplied. If necessary, a new system may be applied to another site. The original treatment schedule should be maintained.

Initiation of Therapy
For treatment of moderate-to-severe vasomotor symptoms, vulvar and vaginal atrophy associated with the menopause, hypogonadism, castration, or primary ovarian failure, treatment is usually initiated with **Alora** 0.05 mg/day applied to the skin twice weekly. The lowest dose and regimen that will control symptoms should be chosen and medication should be discontinued as promptly as possible. Attempts to discontinue or taper medication should be made at 3-month to 6-month intervals.

For the prevention of postmenopausal osteoporosis, the minimum dose of Alora that has been studied and shown to be effective is 0.025 mg/day applied to the skin twice weekly. Bone mineral density measurements should be repeated to monitor treatment efficacy. The dosage may be increased as necessary, depending on bone mineral density and adverse events.

In women who are not currently taking oral estrogens or in women switching from topical therapy or another transdermal estradiol therapy, treatment with **Alora** can be initiated at once. In women who are currently taking oral estrogens, treatment with **Alora** should be initiated one week after withdrawal of oral therapy or sooner if menopausal symptoms reappear in less than one week.

Therapeutic Regimen
Alora may be administered in a continuous regimen in patients who do not possess an intact uterus. In those patients with an intact uterus who are not using concomitant progestin therapy, **Alora** can be administered on a cyclic schedule (e.g. Three weeks of therapy followed by one week without) for the treatment of postmenopausal symptoms. However, no studies have been conducted using this intermittent regimen for the prevention of postmenopausal osteoporosis.

HOW SUPPLIED

Alora 0.025 mg/day (estradiol transdermal system). Each 9 cm^2 system contains 0.75 mg of estradiol USP for nominal delivery of 0.025 mg of estradiol per day when dosed in a twice weekly regimen.
NDC 52544-884-08 Patient Calendar Box of 8 Systems
NDC 52544-884-23 Patient Calendar Box of 24 Systems

Alora 0.05 mg/day (estradiol transdermal system). Each 18 cm^2 system contains 1.5 mg of estradiol USP for nominal delivery of 0.05 mg of estradiol per day when dosed in a twice weekly regimen.
NDC 52544-471-08 Patient Calendar Box of 8 Systems
NDC 52544-471-23 Patient Calendar Box of 24 Systems

Alora 0.075 mg/day (estradiol transdermal system). Each 27 cm^2 system contains 2.3 mg of estradiol USP for nominal delivery of 0.075 mg of estradiol per day when dosed in a twice weekly regimen.
NDC 52544-472-08 Patient Calendar Box of 8 Systems

Alora 0.1 mg/day (estradiol transdermal system). Each 36 cm^2 system contains 3.0 mg of estradiol USP for nominal delivery of 0.1 mg of estradiol per day when dosed in a twice weekly regimen.
NDC 52544-473-08 Patient Calendar Box of 8 Systems

Store at 15° - 30°C (59° - 86°F).
Do not store unpouched. Apply immediately upon removal from the protective pouch.
Discard used **Alora** in household trash in a manner that prevents accidental application or ingestion by children, pets, or others.

Distributed by: Watson Pharma, Inc.
a subsidiary of Watson Laboratories, Inc.
Corona, CA 92880

REVISED MONTH/YEAR

Estradiol Matrix
Transdermal Delivery System
NDA 21-310

Patient Package Insert

Watson Laboratories Inc.
Research Park
417 Wakara Way
Salt Lake City, UT 84108 USA

Patient Information

This leaflet describes the risks and benefits of treatment with Alora® (ah-LORE-ah). Read this information before treatment. Read the information you get each time you get medicine because there may be new information. Talk with your healthcare provider if you have any questions about this medicine.

What Is the Most Important Information I Should Know About Alora?

ESTROGENS INCREASE THE RISK OF CANCER OF THE UTERUS
If you use any estrogen-containing medicine, it is important to visit your healthcare provider regularly and report any unusual vaginal bleeding right away. Vaginal bleeding after menopause may be a warning sign of uterine cancer. Your healthcare provider should check any unusual vaginal bleeding to find out the cause. Women who do not have a uterus have almost no risk of endometrial cancer.

What is Alora?
Alora is a patch that contains the estrogen hormone estradiol. When applied to the skin as directed below, the Alora patch releases estrogen through the skin into the abdomen.

Alora Is Used In The Following Ways:

- **To reduce moderate or severe menopausal symptoms.**
  Estrogens are hormones made by a woman's ovaries. Between ages 45 and 55, the ovaries normally stop making estrogens. This drop in body estrogen levels causes the "change of life" or menopause (the end of monthly menstrual periods). Sometimes, both ovaries are removed during an operation before natural menopause takes place. The sudden drop in estrogen levels causes "surgical menopause."

  When estrogen levels begin dropping, some women develop very uncomfortable symptoms, such as feelings of warmth in the face, neck, and chest, or sudden intense episodes of heat and sweating ("hot flashes" or "hot flushes"). In some women the symptoms are mild and in others they can be severe. Using estrogen drugs can help the body adjust to lower estrogen levels and reduce these symptoms. Most women have only mild menopausal symptoms or none at all, and do not need estrogen therapy for these symptoms. Other women may need to take estrogens for a few months while their bodies adjust to lower estrogen levels. Most women do not need estrogen replacement therapy for longer than six months for these symptoms.

- **To treat itching, burning, and dryness in and around the vagina due to menopause**.

- **To treat certain conditions in which a young woman's ovaries do not produce enough estrogen naturally.**

- **To help reduce your chances of getting osteoporosis (thin weak bones).**
  Osteoporosis is a thinning of the bones that makes them weaker and allows them to break more easily. Women who have menopause at an early age, are thin, smoke or have a family history of osteoporosis are more likely to develop osteoporosis.

  Alora may be used as part of a program which includes weight-bearing exercise like walking and running and taking calcium and vitamin D supplements to reduce your chances of getting osteoporosis. Before you change your exercise habits or calcium or vitamin D intake, it is important to discuss these lifestyle changes with your healthcare provider to find out if they are safe for you. You and your healthcare provider have agreed that you should take Alora to reduce your chances of getting osteoporosis. You may need to take Alora for a long period of time. Before you make any change in your use of Alora, talk with your healthcare provider.

Who Should Not Use Alora

Do not use Alora if you

- **think you may be pregnant**. Using Alora while you are pregnant may harm your unborn child. Do not use Alora to prevent miscarriage.

- **have unusual vaginal bleeding.** If you develop vaginal bleeding while using Alora talk with your healthcare provider about proper treatment.

- **have or have had certain cancers.** Estrogens may increase the risk of certain types of cancer, including cancer of the breast or uterus. If you have or have had cancer, talk to your healthcare provider about the use of Alora.

- **have circulation problems.** Talk with your healthcare provider about your condition. Do not use Alora if you have blood clots or have had them in the past.

- **have recently had a baby.** Do not use Alora to stop your breasts from filling with milk after a baby is born.

- **are allergic to Alora or any of the ingredients in it.**

What Are the Possible Risks and Side Effects of Alora?

Common side effects include:

- Headache.
- Nausea and vomiting.
- Breast tenderness or enlargement.
- Retention of excess fluid. This may make some conditions worsen, such as asthma, epilepsy, migraine, heart disease, or kidney disease.
- Vaginal spotting or bleeding.

Less common but serious effects include:

- Cancer of the uterus.
- Cancer of the breast.
- Gallbladder disease.
- Abnormal blood clotting.

These are some of the warning signs of serious effects:

- Unusual vaginal bleeding.
- Breast lumps.
- Pains in your legs.
- Severe headache and vomiting.
- Dizziness and faintness.
- Changes in vision or speech.

If you have any of these warning signs, or other unusual symptoms that concern you, call your healthcare provider right away.

What Can I Do to Lower My Chances of Getting a Serious Side Effect with Alora?

If you use **Alora**, you can reduce your risks by doing these things:

- **See your healthcare provider regularly.**

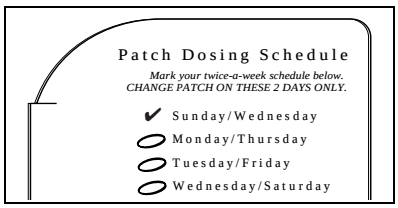
While you are using **Alora**, it is important to visit your healthcare provider at least once a year for a check-up. If you develop vaginal bleeding while taking **Alora**, you may need further evaluation. If members of your family have had breast cancer or if you have ever had breast lumps or an abnormal mammogram (breast x-ray), you may need to have more frequent breast examinations.

How should I use Alora?

Before you begin, read <u>all</u> the information in these 5 steps.

Step 1. Choose your schedule for twice-a-week application.

Put on a new patch twice a week. Use one of the schedules on the inside flap of the patch box.



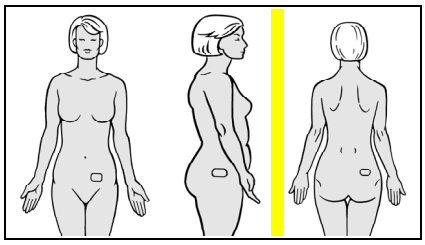
For example, if you apply your first patch on Sunday, take that patch off on Wednesday and put on a new one. Stay on this schedule as long as you use **Alora**. To help remind yourself, mark the schedule on the inside flap of the patch box. Put a check next to the first day you apply the patch. When you change your patch, don't put the new one in the same place. To help reduce the chance of skin redness or irritation, wait at least one week before you reuse a spot.

Step 2 Before you apply the patch

- Make sure the skin at the spot is:
- Freshly washed, but **dry and cool** (wait a few minutes after taking a hot bath or shower).
- Free of body powder or lotion.
- Free of cuts, rashes, or any other skin problem.

Step 3 Choose a spot for the patch

- **Place the patch on the lower abdomen (below the panty line) when you first start using Alora.**

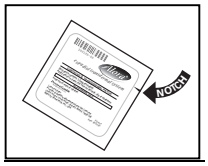


lower abdomen hips buttocks

- As you get used to applying **Alora**, you may want to try the hips or buttocks to see which area works best for you.
- Do not apply **Alora** to your breasts or any other parts of your body.

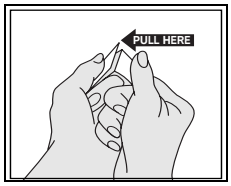
Step 4 How to apply the patch

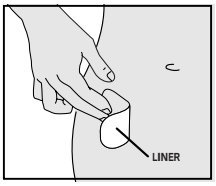
- Open the pouch that contains the patch.



  - Locate the notch on the top left or right corner of the pouch.
  - Hold the pouch at the notch and tear off the top edge. Do not cut the pouch with scissors, which might damage the patch inside.
  - Pull the patch out.

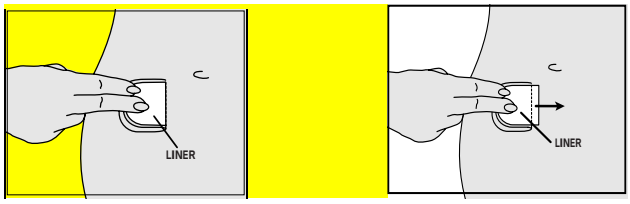
- **<u>Apply one half of the patch to your skin.</u>**





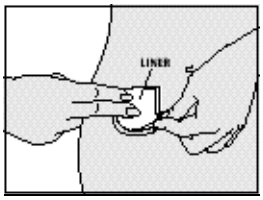
  - Remove half of the liner, which covers the sticky surface of the patch. To find the liner, bend the patch in half. Then grab the clear straight edge of the liner and pull that piece off.
  - Without touching the sticky surface, press the sticky half of the patch onto your skin. (If you touch the sticky surface, the patch may not stay on as well.)
  - Rub the sticky half firmly to ensure full contact with your skin.

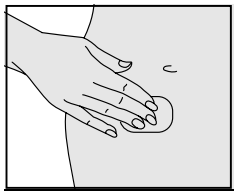
- **<u>Apply the second half of the patch to your skin</u>.**



  - Bend the patch back over itself. Press down on the liner firmly.

  - Push the liner forward a little to loosen the edge.





  - Grab the loose edge at either corner and peel off the second piece of the liner. Try not to touch the sticky surface of the patch.

  - **<u>Press the entire patch firmly onto the skin with your finger tips</u>.**

Press for at least 10 seconds to make sure the patch will stay in place. Be sure all of it sticks to your skin, even around the edges.

To help the patch stay in place:
- Try not to disturb the patch while putting on and removing clothes. It may help to place the patch where your underwear will cover it at all times.
- Be careful while changing clothes, washing or drying off, so that you do not catch the patch with your clothes or the towel.
- Try different sites on the lower abdomen, hips, or buttocks area to see what works well with your body and your clothing.
- If the patch starts to lift, simply press it back in place.

Step 5 Removing the patch
- **Take off the old patch.**
- **Fold it in half (sticky sides together) and throw it away out of the reach of children and pets.**

The skin under the old patch may look pink, but the color should fade away soon. In some cases, the skin may itch or look red; this may last from a couple of hours to a couple of days. Most of the time this is minor, and goes away by itself. But if it bothers you a lot or lasts longer than a few days, call your healthcare provider.

For Best Results, Stay with Your Patch Program
- **Replace your patch twice each week, on the two days you have chosen**. Until it becomes a habit, try:
  - Marking your schedule on the inside flap of the patch box;
  - Marking the days on your calendar;

SU	M	TU	W	TH	F	SA
Alora			Alora			

  - Linking the days you change your patch to other things that always happen on those days (e.g., an exercise class, meetings, etc.)

- **Handle each patch with care**.
  - Make sure the skin is clean, dry, and free of lotion and powder.
  - Try to avoid touching the sticky surface when applying the patch.
  - Be careful while changing clothes, washing or drying off, so that you do not catch the patch with your clothes or the towel.
  - If the patch starts to lift, simply press it back in place.

- **Keep working with your healthcare provider, pharmacist, or other health care professional**. Ask questions. If you have concerns, talk them over - don't just stop using the patch on your own. Remember, it may take a little time and some experience to get accustomed to using a patch.

- **Get your refills of the Alora patch before your supply runs out**.

How should I store Alora?

Store at 59° - 86°F (15° - 30°C). Do not store patches outside of their pouches. Apply the patch as soon as you take it out of the protective pouch.

General Information about Alora

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Your health care provider has prescribed this drug for you and you alone. Do not give the drug to anyone else. Do not use Alora for conditions for which it was not prescribed.

This leaflet provides a summary of the most important information about Alora. If you would like more information, talk with your healthcare provider. You can ask for information about Alora that is written for health professionals. You can also get more information by calling the toll free numbers 1-888-ALORA-4-U (1-888-256-7248).

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

David Orloff

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